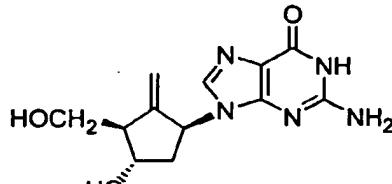


CLAIMS

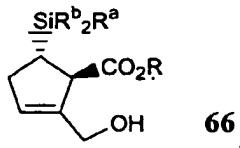
The invention claimed is:

1. A process for the preparation of entecavir having the formula



21, comprising:

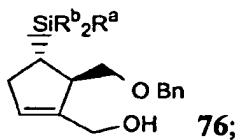
5 (a) treating an ester of the formula



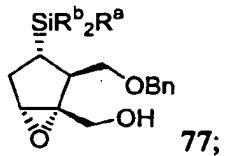
wherein R^a is allyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl; R^b is C₁ to C₆ alkyl; and R is C₁ to C₄ alkyl or benzyl;

with an enol ether of acetone and an acid to protect the hydroxy group,

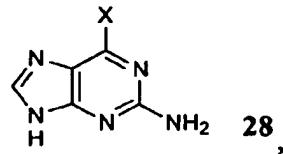
10 followed by treatment with a hydride reagent to reduce the carboxylic acid ester moiety, and then alkylating the resulting alcohol with a benzyl halide and removing the enol ether hydroxy protecting group to give an allylic alcohol of the formula



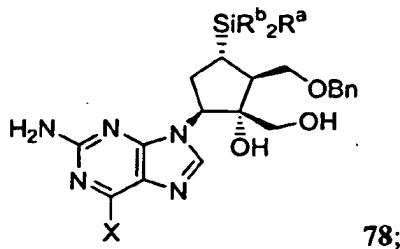
15 (b) epoxidizing the product from step (a) with a diastereoselective epoxidation to give a cyclopentane epoxide having the formula



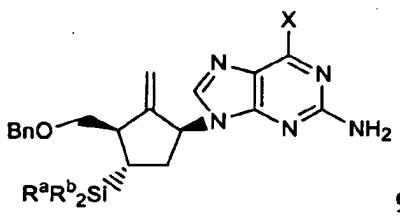
(c) treating the cyclopentane epoxide from step (b) with an alkali metal salt of a purine compound of formula



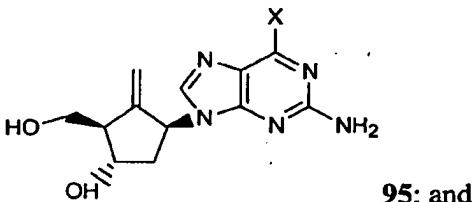
wherein X is Cl, I, or benzyloxy, to give a compound of formula



5 (d) when X is Cl or I, converting the vicinal diol of formula 78 to the methylene compound of formula,

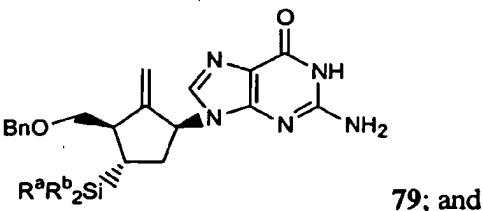


10 (e) hydrolyzing the benzyl ether moiety on the primary alcohol of compound 94 and converting the silane moiety of compound 95 to a hydroxy moiety to give a compound of formula,



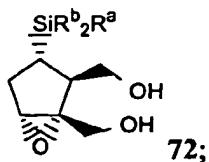
(f) hydrolyzing the chloro or iodo moiety X to provide the compound of formula 21; or

(d') when X is benzyloxy, converting the vicinal diol of formula 78 to the methylene compound of formula

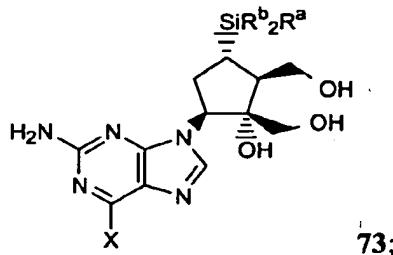


15 (e') hydrolyzing the benzyl ether moiety on the primary alcohol of compound 79 and converting the silane moiety to a hydroxy moiety to provide the compound of formula 21; or

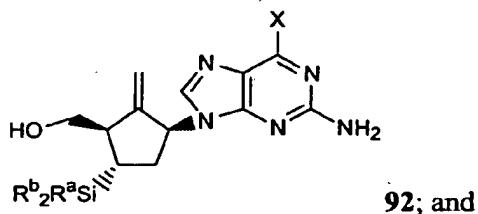
(a'') epoxidizing the ester of formula 66 with a diastereo selective expoxidation, to give a cyclopentane epoxide having the formul



5 (b'') treating the cyclopentane epoxide from step (a'') with an alkali metal salt of the purine compound of formula 28 to give a compound of formula

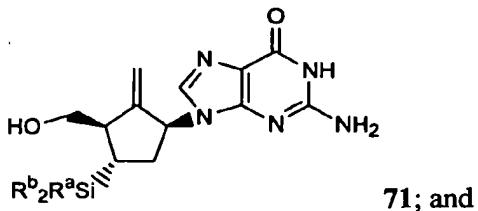


(c'') when X is Cl or I, converting the vicinal diol of formula 73 to the methylene compound of formula



10 (d'') converting the silane moiety of compound 92 to a hydroxy moiety and hydrolyzing the chloro or iodo moiety X to provide the compound of formula 21; or

(c''') when X is benzyloxy, converting the vicinal diol of formula 73 to the methylene compound of formula

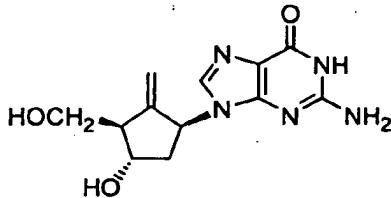


15 (d''') converting the silane moiety of compound 71 to a hydroxy moiety to provide the compound of formula 21.

2. The process of Claim 1, in which, in steps (b) and (a''), the diastereoselective epoxidation is performed with a peracid or with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst.

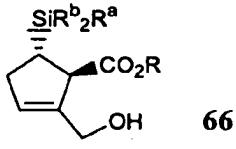
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3. A process for the preparation of entecavir having the formula

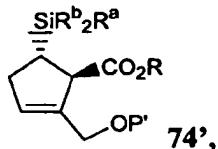


21, comprising:

(a) protecting the hydroxy moiety of an ester of the formula

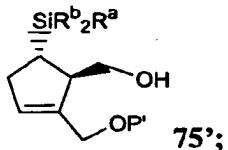


10 wherein R^a is allyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl; R^b is C₁ to C₆ alkyl; and R is C₁ to C₄ alkyl or benzyl, to provide a compound of formula



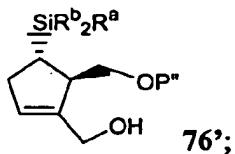
wherein P' is a protecting group;

15 (b) reducing the carboxylic ester moiety of the compound 74' with at least one reducing reagent to provide a compound of formula,

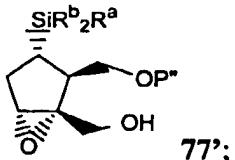


(c) protecting the unprotected hydroxy moiety of compound 75', with a protecting group P'' that is resistant to conditions used to remove P', then removing

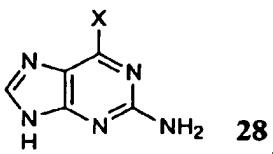
the protecting group P' of the compound of 75', to provide the compound having the formula,



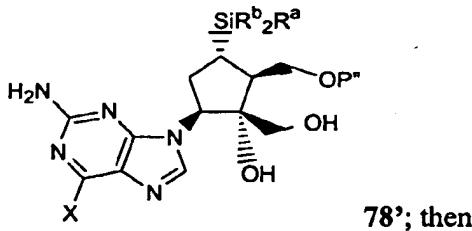
5 (d) epoxidizing the product from step (c) with a diastereoselective epoxidation to give a cyclopentane epoxide having the formula



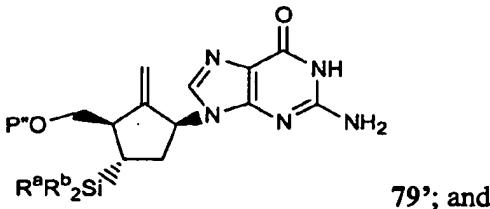
(e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula



10 wherein X is Cl, I, or benzyloxy; to give a compound of formula

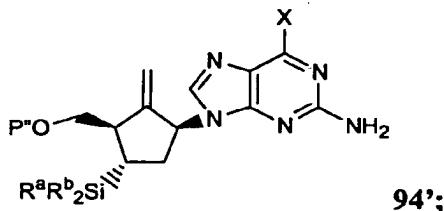


(f) when X is benzyloxy, converting the vicinal diol of formula 78' to provide the methylene compound of formula

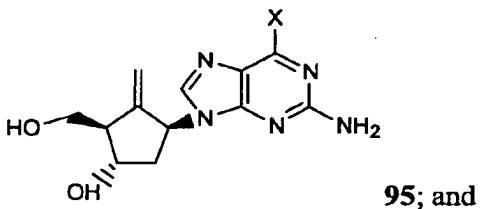


15 (g) removing the protecting group P'' on the primary alcohol of compound 79 and converting the silane moiety to a hydroxy moiety to provide the compound of formula 21; or

(f) when X is Cl or I, converting the vicinal diol of formula 78' to provide the methylene compound of formula,



5 (g') removing the protecting group P'' on the primary alcohol of compound 94' and converting the silane moiety to a hydroxy group to give a compound of formula,



10 (h') hydrolyzing the chloro or iodo moiety X to provide the compound of formula 21.

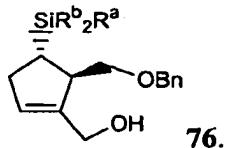
4. The process of Claim 3, wherein, in step (g), the protecting group P'' on the primary alcohol of compound 79' is benzyl, said step of converting the silane 15 moiety of compound 79 to a hydroxy group is achieved with protodesilylation and oxidation, and said benzyl protecting group is removed upon protodesilylation.

5. The process of Claim 3, wherein the protecting group P'' on the primary alcohol of compound 79' is removed after the silane moiety is converted to a hydroxy 20 moiety.

6. The process of Claim 3, wherein in step (a), the hydroxy moiety is protected as a MOP by treatment with 2-methoxypropene and a catalytic amount of a weak acid.

7. The process of Claim 3, wherein in step (b), the carboxylic ester moiety of the compound 74' is reduced with a hydride reagent selected from at least one of sodium bis(2-methoxyethoxy)aluminum hydride and lithium aluminum hydride in the presence of a base.

8. The process of Claim 3, wherein in step (c), the unprotected hydroxy moiety is protected as a benzyl ether upon treatment with a base and a benzyl halide, wherein, removal of the protecting group P' of the compound of 75' provides the 10 allylic alcohol having the formula,



9. The process of Claim 8, wherein the base is selected from at least one of potassium *tert*-butoxide, sodium hydride, KHMDS, and aqueous NaOH, and the 15 benzyl halide is benzyl bromide or benzyl chloride.

10. The process of Claim 3, in which in step (d), the diastereoselective epoxidation is performed by treatment with a peracid.

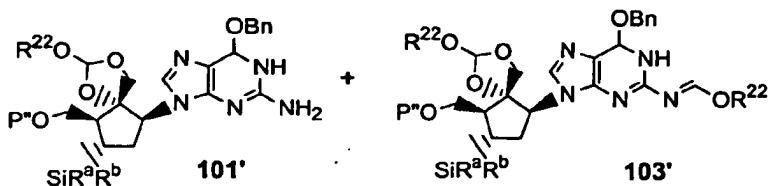
20 11. The process of Claim 3, in which in step (d), the diastereoselective epoxidation is performed by treatment with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst

25 12. The process of Claim 11, wherein the homochiral diester of tartaric acid is (-)-diisopropyl tartrate, the hydroperoxide is *tert*-butylhydroperoxide or α,α -dimethylbenzylhydroperoxide, and the metal catalyst is titanium (IV) isopropoxide.

13. The process of Claim 3, wherein in step (e), the cyclopentane epoxide from step (d) is treated with 2-amino-6-benzyloxypurine in dichloromethane.

14. The process of Claim 3, wherein X is benzyloxy and in step (f), the compound 78' is converted to the methylene compound of formula 79' by

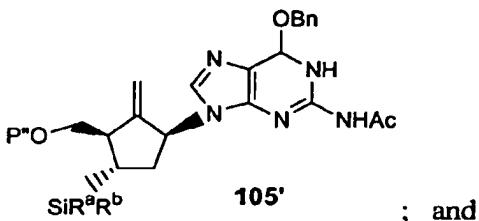
5 (f)(i) treating compound 78' with an orthoformate derivative in an inert solvent to produce a diastereomixture of dioxolanes having the formulae 101' and 103',



10

wherein R²² is C₁₋₄alkyl or -C(=O)C₁₋₄alkyl;

(f)(ii) treating the product from step (f)(i) with an acetic anhydride in the presence of at least one antioxidant to produce an alkene compound having the formula 105';



15

(f) (iii) treating the product from step (f)(ii) with an acid to hydrolyze the 6-benzyloxy and N-acetyl groups to provide the compound of formula 79'.

15. The process of Claim 14, wherein in step (f)(i), the orthoformate derivative is selected from at least one of diethoxymethyl acetate, 20 diisopropylloxymethyl acetate, TMOF, TEOF, and TiPOF.

16. The process of Claim 14, wherein in step (f)(ii), at least one antioxidant is selected from BHT and benzoic acid.

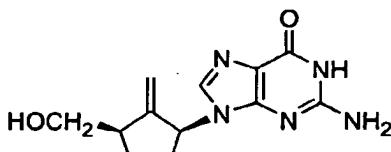
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17. The process of Claim 3, in which the step of converting the compound 79' to compound 21 is achieved with protodesilylation and oxidation, wherein the protodesilylation is performed with KOH or NaOH in solvent, or with TFA, and the 5 primary alcohol moiety is deprotected after the silane moiety is converted to a hydroxy group, to provide the compound of formula 21.

18. The process of Claim 3, in which the step of converting the compound 79' to compound 21 is achieved with protodesilylation and oxidation, wherein the step 10 of protodesilylation is achieved with at least one acid selected from boron trifluoride-acetic acid complex and a Bronsted acid.

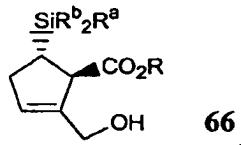
19. The process of Claim 3, in which the step of converting the compound 79' to compound 21 is achieved with protodesilylation and oxidation, and the 15 oxidation is achieved with hydrogen peroxide in the presence of potassium bicarbonate and optionally potassium fluoride.

20. A process for the preparation of entecavir having the formula

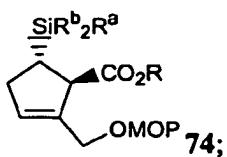


21, comprising:

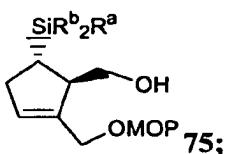
20 (a) treating an ester of the formula



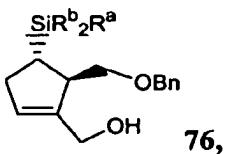
wherein R^a is allyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl; R^b is C₁ to C₆ alkyl; and R is C₁ to C₄ alkyl or benzyl; with 2-methoxypropene and a catalytic amount of a weak acid to provide a compound of formula



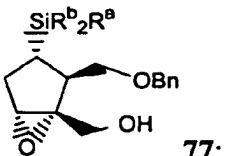
5 (b) reducing the carboxylic ester moiety of the compound 74 with a hydride reagent selected from at least one of sodium bis(2-methoxyethoxy)aluminum hydride and lithium aluminum hydride, in the presence of a base to provide a compound of formula,



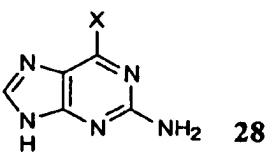
(c) protecting the unprotected hydroxy moiety of compound 75, as a benzyl ether upon treatment of compound 75 with a base and a benzyl halide, then removing the MOP group of the compound 75, to provide the allylic alcohol having the formula,



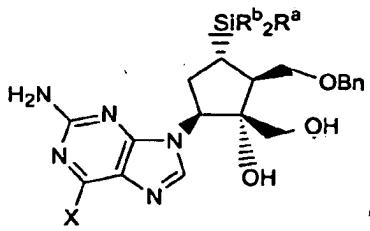
(d) epoxidizing the product from step (c) with (-)-diisopropyl tartrate, *tert*-butylhydroperoxide or cumene hydroperoxide, and titanium (IV) isopropoxide, to give a cyclopentane epoxide having the formula



15 (e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula

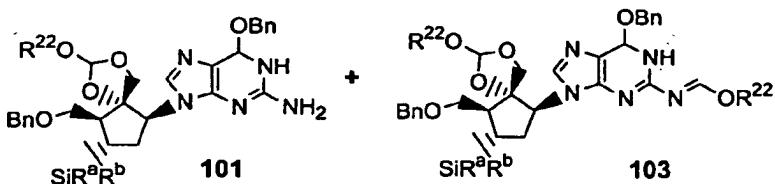


wherein X is benzyloxy; to give a compound of formula



78;

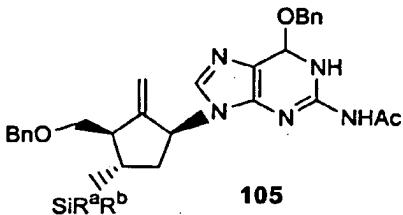
(f)(i) treating compound 78 with an orthoformate derivative selected from diethoxymethyl acetate and diisopropylloxymethyl acetate in an inert solvent to produce a diastereomixture of dioxolanes having the formulae 101 and 103,



5

wherein R²² is ethyl, -C(=O)ethyl, isopropyl, or -C(=O)isopropyl;

(f)(ii) treating the product from step (f)(i) with an acetic anhydride in the presence of BHT to produce an alkene compound having the formula 105;

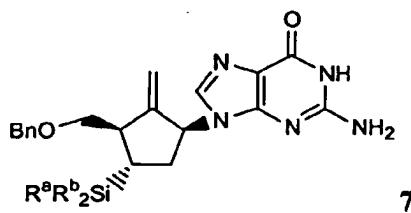


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105

; and

(f) (iii) treating the product from step (f)(ii) with an acid to hydrolyze the 6-benzyloxy and N-acetyl groups and provide the compound of formula 79,



79:

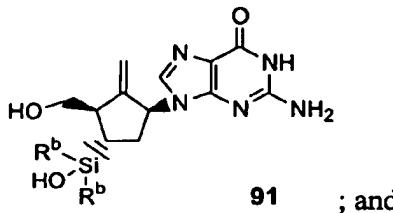
15

(g) converting the silane moiety to a hydroxy moiety by protodesilylating the silane moiety of compound 79 upon treatment with at least one reagent effective to

achieve protodesilylation, followed by oxidation with a peroxide, and debenzylating compound 79, wherein debenzylation may be achieved upon protodesilylation, to provide the compound of formula 21.

5 21. The process of Claim 20, in which step (g) comprises treating compound 79 with an acid selected from boron trifluoride-acetic acid complex and a Bronsted acid, wherein said step of protodesilylation removes the benzyl protecting group of compound 79 to provide the compound of formula 91,

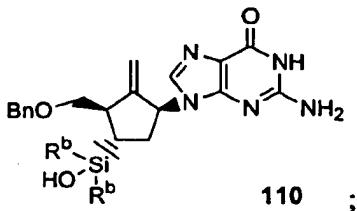
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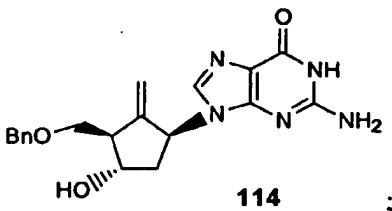
oxidizing the compound 91 with hydrogen peroxide in the presence of potassium bicarbonate and potassium fluoride to provide the compound 21.

22. The process of Claim 20, in which step (g) comprises treating compound 15 79 with potassium hydroxide or sodium hydroxide in solvent, or TFA to provide the compound of formula 110,

20



oxidizing compound 110 with hydrogen peroxide in the presence of potassium bicarbonate and potassium fluoride to provide the compound 114;



and debenzylating compound 114 to provide compound 21.

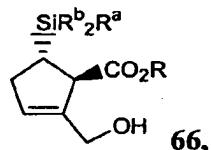
23. A method for isolating entecavir or an entecavir intermediate from a diluted mixture, the diluted mixture comprising entecavir and water or a mixture 5 comprising an entecavir intermediate and other process reagents comprising:

- adsorbing the diluted mixture onto a hydrophobic resin bed;
- washing the resin bed with water to remove salt; and
- eluting the entecavir or entecavir intermediate from the resin bed with an organic solvent.

10

24. The method of Claim 23 wherein the hydrophobic resin is a brominated styrene based resin.

25. A process for the preparation of an ester of the formula



wherein R^a is alkyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl; R^b is C₁ to C₆ alkyl; and R is C₁ to C₄ alkyl or benzyl comprising:

- reacting a cyclopentadienide ion

with a silylating reagent having the formula R^a(R^b)₂Si-Y, wherein Y is a leaving group; and

- reacting the product of step (a) with a ketene to give a cyclobutanone of the formula

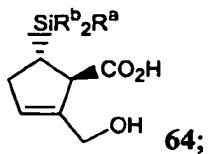
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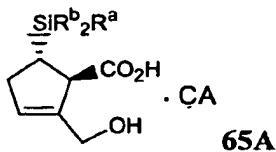
63;

- treating the product from step (b) with a base effective for opening the cyclobutanone ring;

(d) reducing the product from step (c) with a reducing agent to give a racemic carboxylic acid of the formula



5 (e) resolving the product from step (d) by treatment with a chiral amine and separation of the resulting diastereomeric salts to give a compound of formula



wherein CA represents a chiral amine; and

10 (f) heating the product from step (e) in a solution of an acidic solution to give the ester product of formula 66.

10

26. The process of Claim 25, in which, in step (b), the ketene is formed from dichloroacetyl chloride and a base.

15 27. The process of Claim 25, in which, in step (c), the base is potassium carbonate in *t*-butanol.

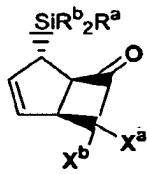
20 28. The process of Claim 25, in which, in step (d), the reducing reagent is NaBH₄.

25 29. The process of Claim 25, in which, in step (e), the chiral amine is selected from the group consisting of R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1R,2R)-(+)-1,2-diphenylethylenediamine, (R)-(-)-1-cyclohexylethylamine, D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, (1S,2S)-(+)-1,2-diaminocyclohexane, dehydroabietylamine, (1R,2R)-1,2-diaminomethylcyclohexane, cichonidine, and cinchonine.

30. The process of Claim 25, in which, in step (f), the acidic solution comprises a solution of an alcohol, R-OH, wherein R is C₁ to C₄ alkyl or benzyl, and an acid.

5 31. The process of Claim 25, in which,
 in step (b), the ketene is formed from dichloroacetyl chloride and a base;
 in step (c), the base is potassium carbonate in *t*-butanol;
 in step (d), the reducing reagent is NaBH₄;
 in step (e), the chiral amine is R,R-(-)-2-amino-1-(4-nitrophenyl)-1,3-
 10 propanediol; and
 in step (f), the acidic solution comprises a solution of an alcohol, R-OH,
 wherein R is C₁ to C₄ alkyl or benzyl, and an acid.

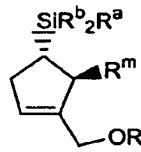
32. A compound of formula



15 wherein:

R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl;
 R^b is C₁ to C₆ alkyl; and
 X^a and X^b are halide.

20 33. A compound of formula



25 OR⁵ or a salt thereof wherein:

R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl;
 R^b is C₁ to C₆ alkyl;
 R^m is -CO₂R⁶ or -CH₂OR⁶;
 R⁵ is hydrogen or a hydroxy protecting group; and
 R⁶ is hydrogen, C₁ to C₄ alkyl, or benzyl.

34. A compound of Claim 33 wherein:

R^m is $-CO_2R^6$; and

R^5 and R^6 are both hydrogen.

5

35. The compound of Claim 34 wherein:

R^a is phenyl; and

R^b is methyl.

10 36. A compound of Claim 33 as a salt with a chiral amine selected from the group consisting of R,R -($-$)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, ($1R,2R$)-($+$)-1,2-diphenylethylenediamine, (R)-($-$)-1-cyclohexylethylamine; D-threo-2-amino-1-(4-nitrophenyl)-1,3-propanediol, ($1S,2S$)-($+$)-1,2-diaminocyclohexane, dehydroabietylamine, ($1R,2R$)-1,2-diaminomethylcyclohexane, cinchonidine, and
15 cinchonine.

37. The compound of Claim 36 wherein:

R^m is $-CO_2R^6$;

R^5 and R^6 are both hydrogen;

20 R^a is phenyl;

R^b is methyl; and

the chiral amine is R,R -($-$)-2-amino-1-(4-nitrophenyl)-1,3-propanediol.

38. The compound of Claim 33 wherein:

25 R^m is $-CH_2OR^6$;

R^5 is hydrogen; and

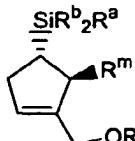
R^6 is benzyl.

39. The compound of Claim 38 wherein:

30 R^a is phenyl; and

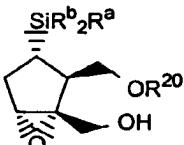
R^b is methyl.

40. A compound having the formula

OR⁵ or a salt thereof wherein:R^a is phenyl;5 R^b is C₁ to C₆ alkyl;R^m is -CO₂R⁶ or -CH₂OR⁶;R⁵ is hydrogen or a hydroxy protecting group; and10 R⁶ is hydrogen, C₁ to C₄ alkyl, or benzyl, said compound produced according to the process of claim 22.

10

41. A compound of formula



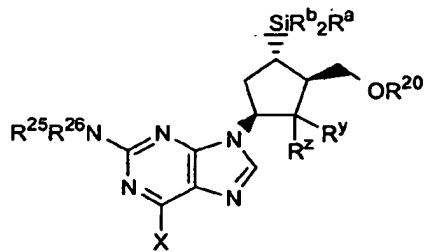
wherein:

R^a is alkyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl;R^b is C₁ to C₆ alkyl; and15 R²⁰ is hydrogen or benzyl.

42. The compound of Claim 41 wherein:

R^a is phenyl;R^b is methyl; and20 R²⁰ is benzyl.

43. A compound of formula



or a salt thereof wherein:

5 R^a is alkyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl;

R^b is C₁ to C₆ alkyl;

R²⁰ is hydrogen or benzyl;

X is Cl, I, or benzyloxy;

10 R^y and R^z are taken together to form methylene (=CH₂), or R^y is OR²³, and R^z is -CH₂OR²⁴, wherein R²³ and R²⁴ are each hydrogen or are taken together to form a ring to define a dioxolane, said dioxolane being optionally substituted with -O(C₁₋₄alkyl) or -O(C=O)(C₁₋₄alkyl); and

15 R²⁵ and R²⁶ are both hydrogen, or one of R²⁵ and R²⁶ is hydrogen and the other is acyl; or R²⁵ and R²⁶ are taken together to form =CH(OC₁₋₄alkyl) or =CH(OC(=O)C₁₋₄alkyl).

44. The compound of Claim 43 wherein:

15 R^a is phenyl;

R^b is methyl; and

X is benzyloxy.

45. The compound of claim 44 in which

20 R²⁰ is benzyl;

R^y is OH, and R^z is -CH₂OH, and

R²⁵ and R²⁶ are both hydrogen.

25 46. The compound of Claim 43 wherein:

R^a is phenyl;

R^b is methyl;

X is benzyloxy;

R^y is OR²³, and R^z is -CH₂OR²⁴, wherein R²³ and R²⁴ combine to form a dioxolane optionally substituted with -O(C₁₋₄alkyl) or O(C=O)(C₁₋₄alkyl); and R²⁵ and R²⁶ are both hydrogen, or R²⁵ and R²⁶ are taken together to form =CH(OC₁₋₄alkyl) or =CH(O(C=O)C₁₋₄alkyl).

5

47. The compound of Claim 43 wherein:

10

R^a is phenyl;

R^b is methyl;

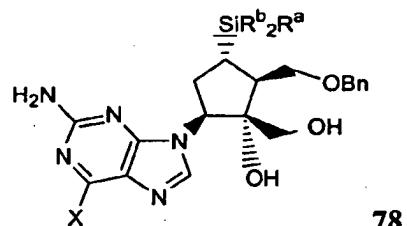
X is benzyloxy;

R^y and R^z are taken together to form methylene; and

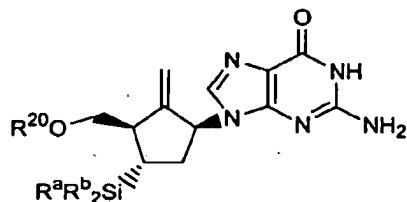
R²⁵ is hydrogen and R²⁶ is acyl.

15

48. The compound of Claim 43 having the formula,



49. A compound of formula



or a salt thereof, wherein:

20

R^a is alkyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl;

R^b is C₁ to C₆ alkyl; and

R²⁰ is hydrogen or benzyl.

50. The compound of Claim 49 wherein:

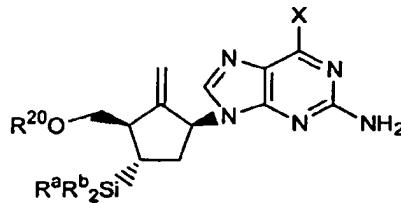
R^a is phenyl;
 R^b is methyl; and
 R^{20} is hydrogen.

5 51. The compound of Claim 49 wherein:

R^a is phenyl;
 R^b is methyl; and
 R^{20} is benzyl.

10 52. The methanesulfonate salt of the compound of Claim 51.

53. A compound of formula

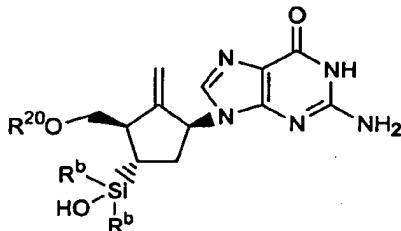


or a salt thereof, wherein:

X is Cl or I;

15 R^a is alkyl, phenyl, C_1 to C_6 alkylphenyl, or C_1 to C_6 alkoxyphenyl;
 R^b is C_1 to C_6 alkyl; and
 R^{20} is hydrogen or benzyl.

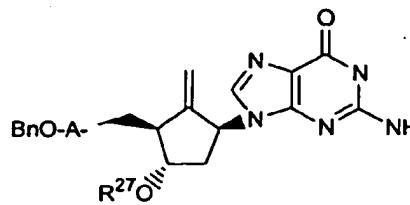
54. A compound of formula



20 wherein R^b is C_1 to C_6 alkyl; and R^{20} is hydrogen or benzyl, or a salt thereof.

55. The compound of Claim 54 wherein R^b is methyl.

56. A compound of formula

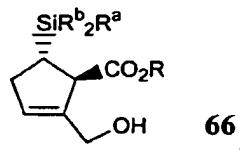
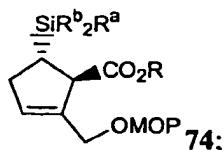


or a salt thereof, wherein:

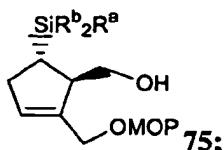
A is CH_2 or a bond;R²⁷ is hydrogen, benzyl, or SiR^d_2R^c ;5 R^c is C₁ to C₄ alkyl or phenyl; andR^d is C₁ to C₃ alkyl.57. A compound of claim 56, in which A is a bond, and R²⁷ is hydrogen.

10 58. A method for making a compound of formula 78, according to Claim 48, comprising,

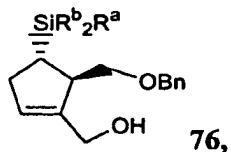
(a) treating an ester of the formula

15 wherein R^a is allyl, phenyl, C₁ to C₆ alkylphenyl, or C₁ to C₆ alkoxyphenyl; R^b is C₁ to C₆ alkyl; and R is C₁ to C₄ alkyl or benzyl; with 2-methoxypropene and a catalytic amount of a weak acid to provide a compound of formula

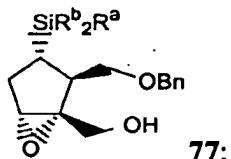
20 (b) reducing the carboxylic ester moiety of the compound 74 with at least one hydride reagent to provide a compound of formula,



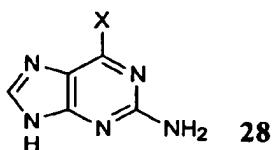
(c) protecting the unprotected hydroxy moiety of compound 75, as a benzyl ether upon treatment of compound 75 with a base and a benzyl halide, then removing the MOP group of the compound 75, to provide the allylic alcohol having the formula,



5 (d) epoxidizing the product from step (c) with a diastereoselective expoxidation, to give a cyclopentane epoxide having the formula

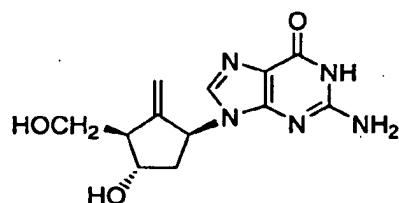


(e) treating the cyclopentane epoxide from step (d) with an alkali metal salt of a purine compound of formula



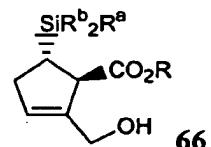
wherein X is benzyloxy; I, or Cl, to give a compound of formula 78.

59. A process for the preparation of entecavir having the formula

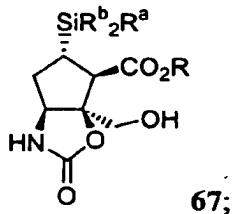


15 21, comprising:

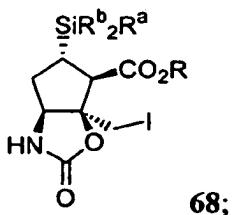
(a) converting an ester having the formula



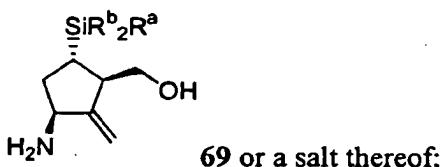
wherein R is C₁ to C₄ alkyl, or benzyl; R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl, and R^b is C₁ to C₆ alkyl, under aminohydroxylation conditions to give an oxazolidinone having the formula



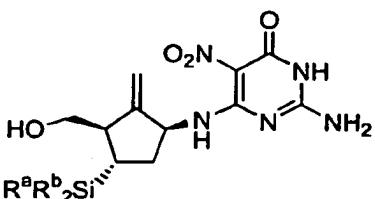
5 (b) converting the alcohol of the oxazolidinone of formula 67 with an iodide salt to give an iodide having the formula



(c) treating the iodide of formula 68 with zinc and acetic acid;
 (d) treating the product of step (c) with a hydride reagent to reduce the ester moiety to an alcohol and give a methylene compound of formula

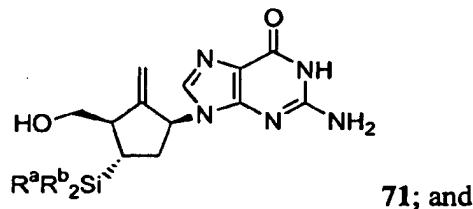


(e) reacting the methylene compound of formula 69 with 6-chloro-2-amino-5-nitro-4(3H)-pyrimidinone in the presence of base to give a pyrimidine compound having the formula



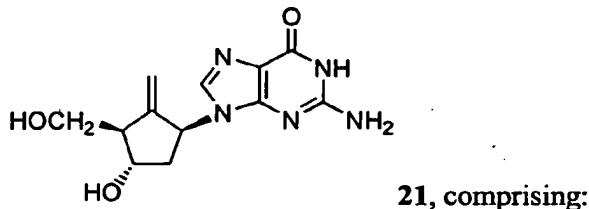
15 (f) treating the pyrimidine compound of formula 70 with a reducing agent to reduce the nitro moiety to an amine;

(g) cyclizing the product of step (f) with an orthoformate derivative and an acid to give a methylene compound having the formula

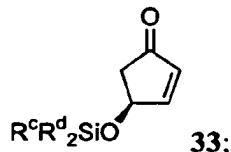


(h) converting the silane moiety of the compound of formula 71 to a hydroxy moiety and providing the compound of formula 21.

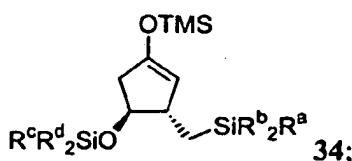
60. A process for the preparation of entecavir having the formula



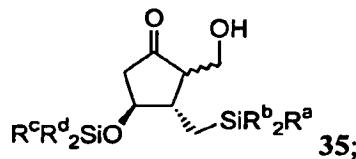
(a) treating 4-(S)-hydroxy-2-cyclopenten-1-one with a silylating reagent of the formula $R^cR^d_2SiY$ and a trialkylamine base wherein R^c is C_1 to C_4 alkyl or phenyl, R^d is C_1 to C_3 alkyl, and Y is a leaving group to give the compound of formula



(b) treating the product from step (a) with a Grignard reagent prepared from a (halomethyl)silane reagent of the formula $R^aR^b_2SiCH_2X'$, wherein R^a is allyl, phenyl, C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl; R^b is C_1 to C_6 alkyl; and X' is chloro, bromo, or iodo followed by treatment with trimethylsilylating reagent to give a compound of formula

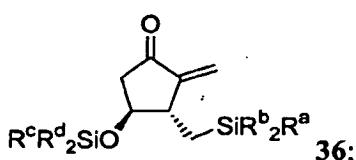


(c) formylating the compound of formula 34 to give a compound of formula

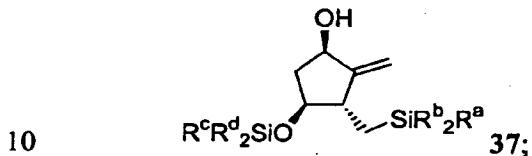


(d) treating the compound of formula 35 with a sulfonylating reagent having the formula $\text{R}^3\text{SO}_2\text{Cl}$, wherein R^3 is C_1 to C_4 alkyl, trifluoromethyl, phenyl or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy;

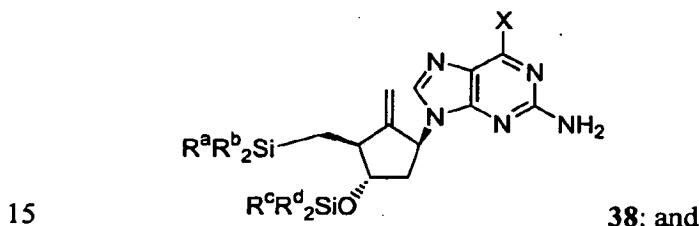
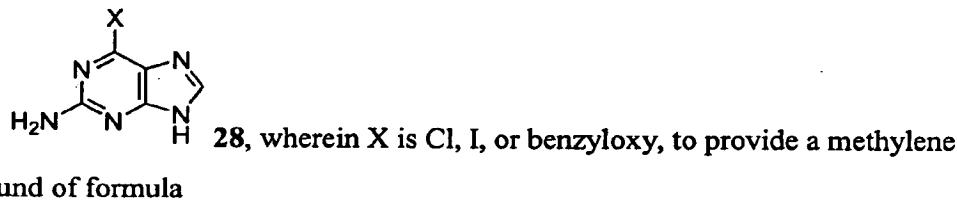
5 (e) reacting the product of step (d) with a strong base to eliminate a sulfonate group to provide a methylene compound of formula



(f) selectively reducing the methylene compound of formula 36 with a hydride reagent to provide an allylic alcohol of the formula

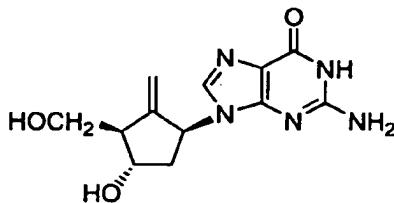


(g) condensing the allylic alcohol of the formula 37 under Mitsonobu conditions with a purine compound of formula



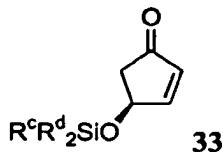
(h) converting the compound of formula 38 to the compound of formula 21.

61. A process for the preparation of entecavir having the formula



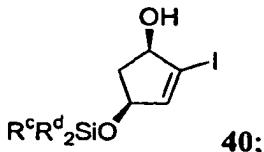
21, comprising:

(a) reacting a cyclopentenone of the formula

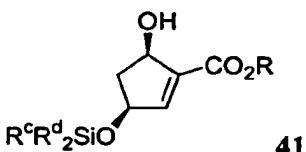


with iodine, wherein R^c is C₁ to C₄ alkyl, or phenyl, and R^d is C₁ to C₃ alkyl;

5 (b) reducing the carbonyl group of the product of step (a) to provide an iodo compound of formula

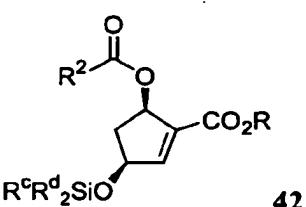


(c) converting the iodo compound of formula 40 to give a compound of formula



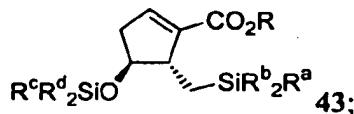
10 wherein R is C₁ to C₄ alkyl, or benzyl;

(d) acylating the compound of formula 41 with an activated acyl agent of the formula R²C(O)-Y wherein R² is C₁ to C₆ alkyl, arylalkyl or aryl, and Y is a leaving group to give a compound of formula

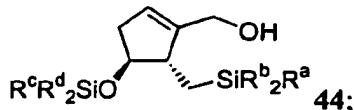


15 (e) treating the product of step (d) with a Grignard reagent prepared from a (halomethyl)silane reagent of the formula R^aR^b₂SiCH₂X', wherein R^a is allyl, phenyl,

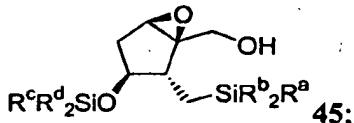
C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl; R^b is C_1 to C_6 alkyl; and X' is chloro, bromo, or iodo to give an ester of the formula



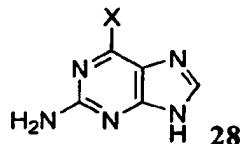
5 (f) reducing the ester of formula 43 with a hydride reagent to provide an allylic alcohol of the formula



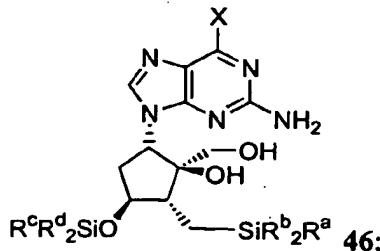
5 (g) epoxidizing the allylic alcohol of formula 44 with an oxidizing agent to provide a cyclopentane epoxide of the formula



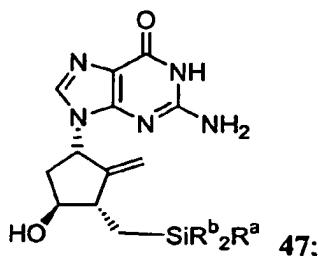
10 (h) reacting the cyclopentane epoxide of formula 45 with an alkali metal salt of a purine compound of formula



wherein X is Cl, I or benzyloxy, to give a compound of formula



15 (i) converting the compound of formula 46 to a methylene compound of formula

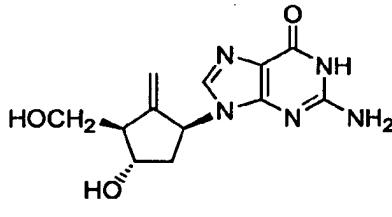


(j) treating the compound of formula 47 with an acid or base effective for protodesilylation of the silyl moiety; and

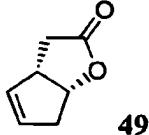
(k) oxidizing the product of step (j) to provide the compound of formula 21.

5

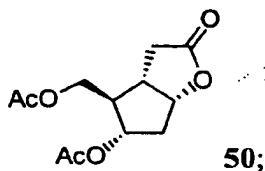
62. A process for the preparation of entecavir having the formula



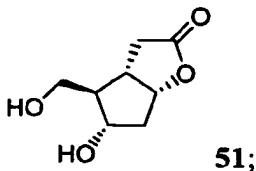
(a) treating a homochiral bicyclic lactone of the formula



10 with paraformaldehyde, acetic acid, and sulfuric acid to provide a diacetate of the formula

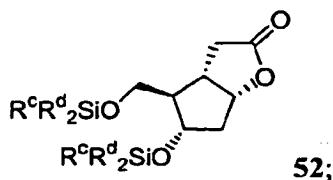


15 (b) treating the diacetate product of step (a) using a base in an alcohol solvent to remove the acetate protecting groups to give the compound having the formula

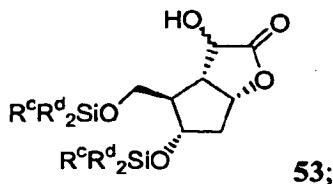


(c) treating the product of step (b) with a silylating reagent of the formula $R^cR^d_2SiY$, wherein R^c is linear or branched C_1 to C_4 alkyl, or phenyl, and R^d is linear or branched C_1 to C_3 alkyl and Y is a leaving group, to provide a compound of formula

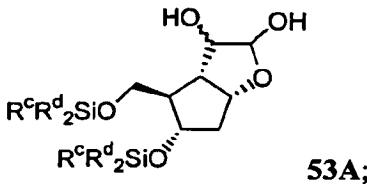
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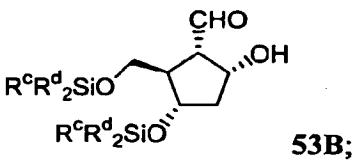
(d) treating the product of step (c) with a strong non-nucleophilic base and (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine to give a compound of formula



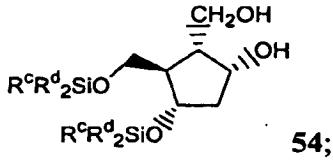
10 (e) reducing the lactone moiety of the product from step (d) with a hydride reagent to give a compound having the formula



(f) cleaving the product from step (e) with an oxidizing agent to give a compound of formula

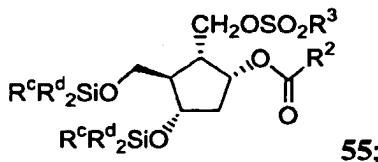


15 (g) reducing the product from step (f) with a hydride reagent to give a diol of the formula

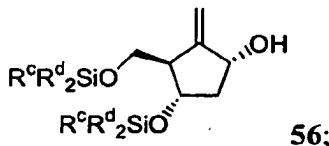


(h) selectively sulfonylating the primary alcohol of the product from step (g) with a reagent of the formula R^3SO_2Cl , wherein R^3 is C_1 to C_4 alkyl, trifluoromethyl, phenyl, or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy;

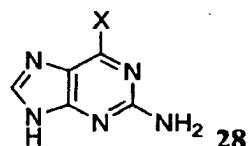
5 (i) acylating the secondary alcohol of the product of step (h) with an acylating agent of the formula $R^2C(O)-Y$, wherein R^2 is C_1 to C_6 alkyl, arylalkyl or aryl, and Y is a leaving group to give a compound having the formula



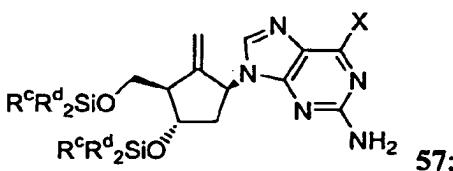
10 (j) treating the product from step (i) with a strong base to effect elimination and hydrolysis of the carboxylic acid ester to give the compound of formula



(k) condensing the product from step (j) with a purine compound of formula



15 wherein X is Cl, I or benzyloxy, under Mitsonobu conditions to give a methylene compound of formula

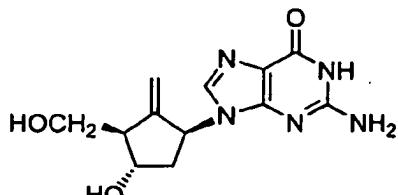


(l) removing the silyl ether protecting groups of the methylene compound of formula 57; and

(m) hydrolyzing the 6-X group to give the compound of formula 21.

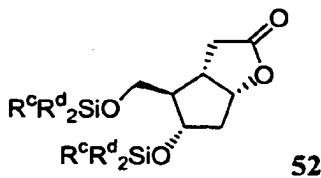
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63. A process for the preparation of entecavir having the formula



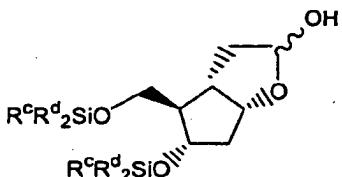
21, comprising:

(a) reducing the compound of formula



52

to give a lactol of the formula

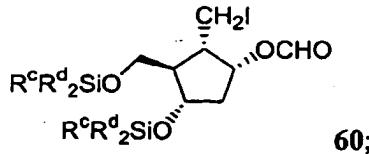


59

5

wherein R^c is a linear or branched C₁ to C₄ alkyl, or phenyl, and R^d is a linear or branched C₁ to C₃ alkyl;

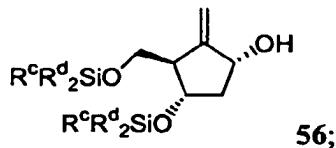
(b) iodinating the lactol product of step (a) by free radical oxidation to give an iodide compound having the formula



10

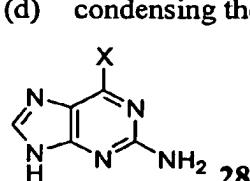
60;

(c) treating the product from step (b) with a strong base to give the methylene compound of formula



56;

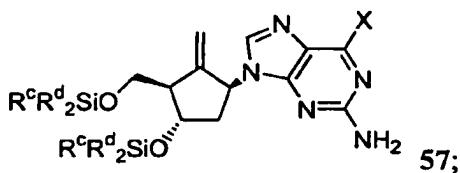
15



28

(d) condensing the product from step (c) with a purine compound of formula

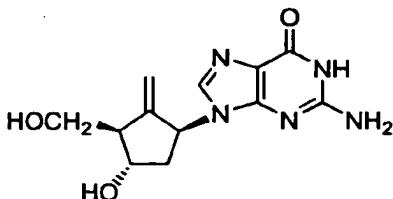
wherein X is Cl, I or benzyloxy, under Mitsonobu conditions to give a methylene compound of formula



5 (e) removing the silyl ether protecting groups of the methylene compound of formula 57; and

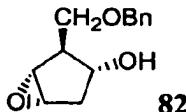
(f) hydrolyzing the 6-X group to give the compound of formula 21.

64. A process for the preparation of entecavir having the formula

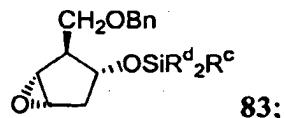


10 21, comprising:

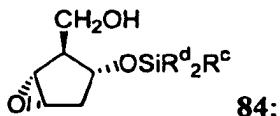
(a) silylating a compound of formula



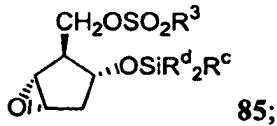
with a compound of formula $R^c R^d 2SiY$, wherein R^c is linear or branched C_1 to C_4 alkyl, or phenyl, R^d is linear or branched C_1 to C_3 alkyl, and Y is a leaving group, to provide a compound of formula



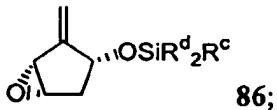
(b) reducing the product from step (a) under conditions sufficient to remove the benzyl protecting group to give a compound of formula



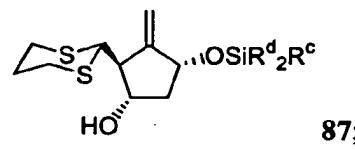
(c) converting the alcohol moiety of the product from step (b) to a sulfonate ester of the formula SO_2R^3 , wherein R^3 is C_1 to C_4 alkyl, trifluoromethyl, or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy to give a compound of formula



5 (d) treating the product from step (c) with a strong base to effect elimination of the $\text{R}^3\text{SO}_3\text{H}$ to provide the methylene compound of formula

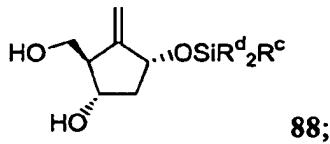


(e) treating the product from step (d) with a lithium salt of 1,3-dithiane to provide the compound of formula

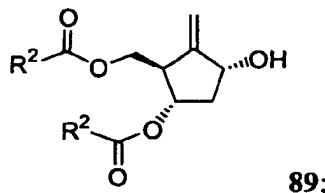


(f) hydrolyzing the dithioacetal moiety of the compound of formula 87; and

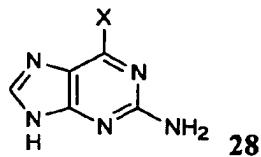
(g) treating the product of step (f) with a hydride reagent to provide a compound of formula



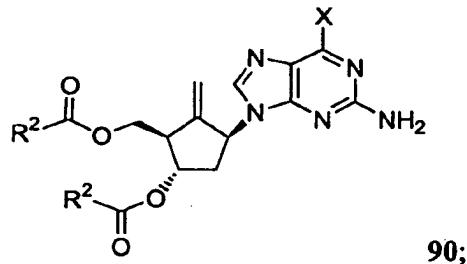
15 (h) acylating the compound of formula 88 with a compound having the formula $\text{R}^2\text{C}(\text{O})-\text{Y}$, wherein Y is a leaving group and R^2 is C_1 to C_6 alkyl or aryl, to give the compound of formula



(i) condensing the product from step (h) with a purine compound of formula

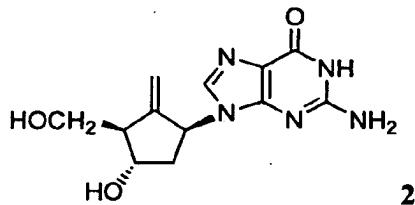


wherein X is Cl, I, or benzyloxy under Mitsonobu conditions to give a methylene compound of formula



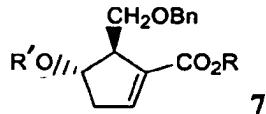
5 (j) removing the acyl ester protecting groups from the methylene compound of formula 90; and
 (k) hydrolyzing the X group to give the compound of formula 21.

10 65. A process of preparing entecavir having the formula



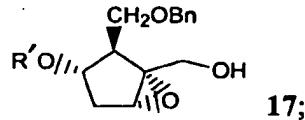
21, comprising:

(a) reducing an ester of the formula

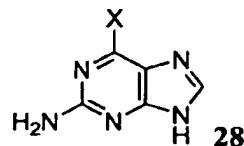


15 wherein R is C₁ to C₄ alkyl, or benzyl, and R' is benzyl, benzyl substituted on the phenyl moiety by C₁ to C₆ alkyl or C₁ to C₆ alkoxy, or R^cR^dSi wherein R^c is linear or branched C₁ to C₄ alkyl or phenyl, and R^d is linear or branched C₁ to C₃ alkyl, with a hydride reagent;

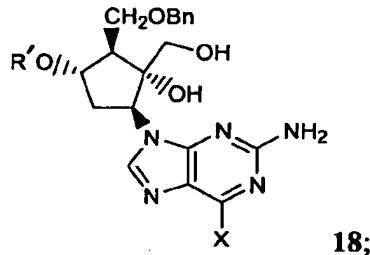
(b) asymmetrically epoxidizing the product from step (a) with a homochiral diester of tartaric acid, a hydroperoxide, and a metal catalyst to provide the cyclopentane epoxide of the formula



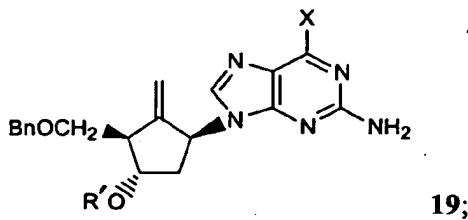
5 (c) treating the product of step (b) with an alkali metal salt of a purine compound of formula



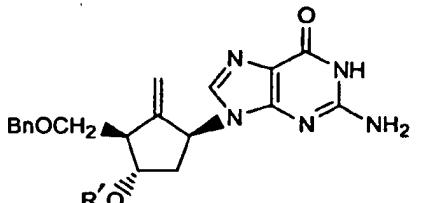
wherein X is Cl, I or BnO, to provide a compound of formula



10 (d) converting the vicinal diol product of step (c) to an alkene to provide the methylene compound of formula

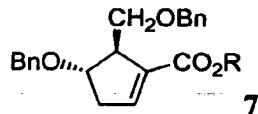


(e) hydrolyzing the X group of the compound of formula 19 to provide the methylene compound of formula



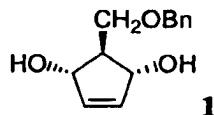
(f) removing the benzyl ether protecting group(s) to provide the compound of formula 21.

5 66. A process for the preparation of an ester of the formula

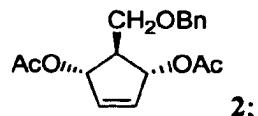


wherein R is C₁ to C₄ alkyl or benzyl, comprising:

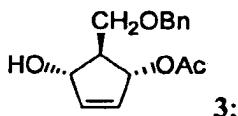
(a) acetylation of a diol of the formula



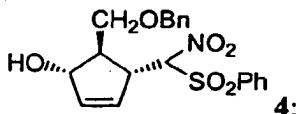
10 with an anhydride to provide the diacetate of the formula



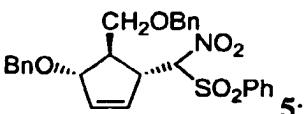
(b) hydrolyzing the product from step (c) with a hydrolase enzyme to give a compound of formula



15 (c) coupling the product from step (b) with phenylsulfonylnitromethane to give a compound of formula

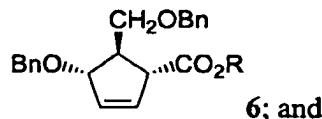


(d) alkylating the product from step (c) with a benzyl halide to provide the compound of formula



20

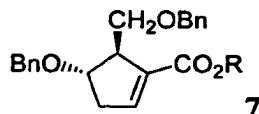
(e) converting the product from step (d) to an ester of the formula



(f) isomerizing the ester of the formula **6** under basic conditions to provide the ester of the formula **7**.

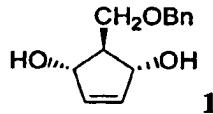
5

67. A process for the preparation of an ester of the formula



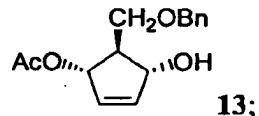
wherein R is C₁ to C₄ alkyl or benzyl, comprising:

(a) asymmetrically acetylating the diol of the formula



10

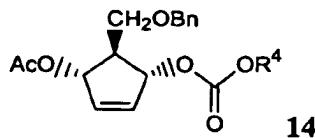
with a C₁ to C₆ alkyl acetate ester and hydrolase enzyme to obtain a compound of formula



15

(b) acylating the product from step (a) to give an alkyl carbonate of the

formula

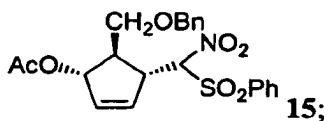


wherein R⁴ is C₁ to C₆ alkyl, benzyl, phenyl, or phenyl substituted by C₁ to C₆ alkyl or C₁ to C₆ alkoxy;

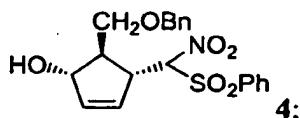
20

(c) coupling the product from step (b) with phenylsulfonylnitromethane to

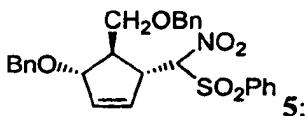
obtain a compound of formula



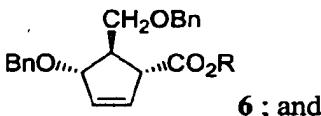
(d) hydrolyzing the product from step (c) with a base to obtain a compound of formula



5 (e) alkylating the product from step (d) with a benzyl halide in the presence of strong non-nucleophilic base to give the compound of formula

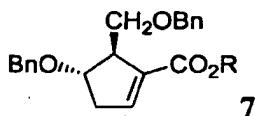


(f) converting the product from step (e) to an ester of the formula



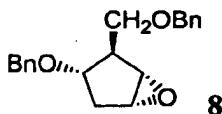
10 (g) isomerizing the ester of the formula 6 under basic conditions to provide the ester of the formula 7.

68. A process for the preparation of an ester of the formula

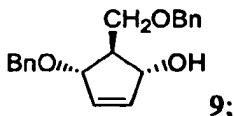


15 wherein R is C₁ to C₄ alkyl or benzyl, comprising:

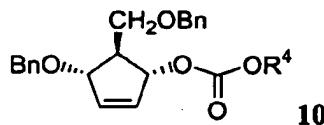
(a) reacting a cyclopentane epoxide of the formula



with a strong non-nucleophilic base to form an allylic alcohol of the formula

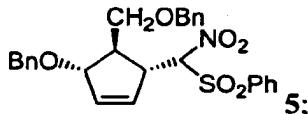


20 (b) acylating the product from step (a) to give an alkyl carbonate ester of the formula

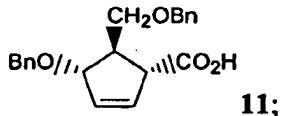


wherein R^4 is C_1 to C_6 alkyl, benzyl, phenyl, or phenyl substituted by C_1 to C_6 alkyl or C_1 to C_6 alkoxy;

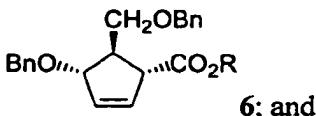
5 (c) coupling the product of step (b) with phenylsulfonylnitromethane to give
the compound of formula



(d) converting the product from step (c) to an acid of the formula

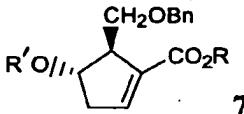


(e) converting the product from step (d) to an ester of the formula



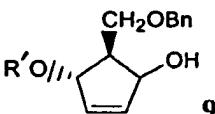
(f) isomerizing the product from step (e) under basic conditions to provide
the ester of formula 7.

15 69. A process of preparing an ester of the formula

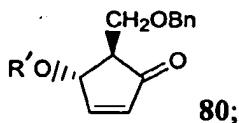


wherein R is C_1 to C_4 alkyl, or benzyl; R' is benzyl, or benzyl substituted on the phenyl moiety by C_1 to C_6 alkyl or C_1 to C_6 alkoxy, or $R^cR^d_2Si$, wherein R^c is C_1 to C_4 alkyl, or phenyl, and R^d is C_1 to C_3 alkyl; comprising:

20 (a) oxidizing an allylic alcohol of the formula

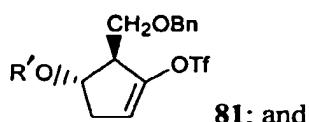


with an oxidizing agent to give a cyclopentenone of the formula



(b) reducing the cyclopentenone of the formula **80** with lithium tri-*sec*-butylborohydride;

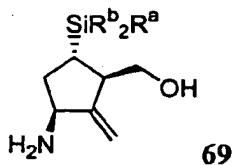
5 (c) sulfonylating the product of step (b) with a triflating reagent to give a compound of formula



(d) converting the triflate moiety of the compound of formula **81** to an alkoxycarbonyl moiety to give the ester of the formula **7**.

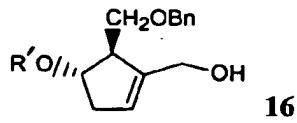
10

70. A compound of formula



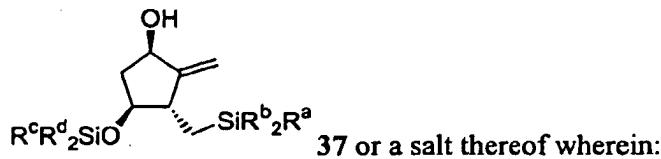
wherein R^a is allyl, phenyl, C_1 to C_6 alkylphenyl or C_1 to C_6 alkoxyphenyl; and R^b is
15 C_1 to C_6 alkyl; or a salt thereof.

71. A compound of formula



or a salt thereof wherein R^1 is benzyl or $R^cR^d_2Si-$, R^c is C_1 to C_4 alkyl or phenyl, and
20 R^d is C_1 to C_3 alkyl.

72. A compound of formula



R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl;

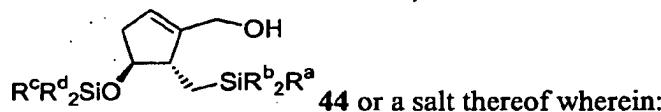
R^b is C₁ to C₆ alkyl;

R^c is C₁ to C₄ alkyl or phenyl; and

R^d is C₁ to C₃ alkyl.

5

73. A compound of formula



10

R^a is allyl, phenyl, C₁ to C₆ alkylphenyl or C₁ to C₆ alkoxyphenyl;

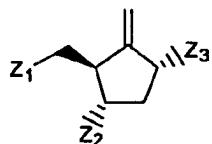
R^b is C₁ to C₆ alkyl;

R^c is C₁ to C₄ alkyl or phenyl; and

R^d is C₁ to C₃ alkyl.

15

74. A compound of formula



wherein Z₁ and Z₂ are both R^cR^dSiO₂⁻ and Z₃ is hydroxy or Z₁ and Z₂ are both hydroxy and Z₃ is R^cR^dSiO₂⁻;

R^c is C₁ to C₄ alkyl or phenyl; and

R^d is C₁ to C₃ alkyl.

20